PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
A61K 9/20, 9/32, 9/48
C08F 8/14, 220/12

A1

(11) International Publication Number: WO 92/07553

(43) International Publication Date: 14 May 1992 (14.05.92)

(21) International Application Number: PCT/EP91/02046

(22) International Filing Date: 24 October 1991 (24.10.91)

(30) Priority data:
9002331 24 October 1990 (24.10.90) NL
9002336 25 October 1990 (25.10.90) NL

(71) Applicant *(for all designated States except US)*: K.U. LEUVEN RESEARCH & DEVELOPMENT [BE/BE]; Groot Begijnhof, Benedenstraat 59, B-3000 Leuven (BE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : KINGET, Renaat, Daniel [BE/BE]; Dorpsstraat 139, B-3060 Bertem (BE). PEETERS, Rita, Maria, Rosa [BE/BE]; Beatrijslaan 99, B-3110 Rotselaar (BE).

(74) Agents: HOIJTINK, Reinoud et al.; Arnold & Siedsma, Octrooibureau, Sweelinckplein 1, NL-2517 GK The Hague (NL).

(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), CS, DE (European patent), DK (European patent), ES (Eur pean patent), FR (European patent), GB (European patent), GR (European patent), HU, IT (European patent), JP, LU (European patent), NL (European patent), NO, PL, SE (European patent), US.

Published
With international search report.

(54) Title: COATING OR MATRIX MATERIAL FOR MEDICAMENTS

(57) Abstract

A coating or matrix material for medicaments, comprising a copolymer of (meth)acrylic acid and alkyl or hydroxyalkyl (meth)acrylate, will have the property of being resistent to gastric juice and dissolving or disintegrating only in the colon if the ratio of free carboxy groups to esterified carboxy groups in the copolymer is between 1:4.5 and 1:3 (the limiting values excluded). Such copolymers may be prepared either by direct copolymerisation of monomers in such proportions that a copolymer having the specified ratio is obtained, or else by starting with a copolymer having a ratio between 1:1 and 1:3 and partially esterifying the free carboxy groups therein to reach the specified ratio.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CI	Côte d'Ivoire	LI	Liechtenstein	SU+	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
DE*	Germany	MC	Monaco	US	United States of America
DK	Denmark				

+ Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

Coating or matrix material for medicaments

This invention relates to a coating or matrix material for medicaments which is resistent to gastric juice and will disintegrate only within the large intestine (colon). Further, it relates to a method of preparing such a coating or matrix material and to medicaments provided with a coating or matrix of that material.

In many cases, it is desirable to coat a medicament in such a way that the active ingredient is only released after a predetermined time interval or after reaching a certain location within the body. Thus, many medicaments for oral administration are provided with a coating or matrix of a material which is resistent to gastric juice but will disolve or disintegrate in the juice of the small intestine, thus allowing the active ingredient to pass the stomach without any hindrance and to be released only in the small intestine to excercise its activity. Materials of this type are commonly indicated as gastric-resistent coating or matrix materials or "enteric coating matrix materials". Suitable examples thereof are: methacrylate polymers and copolymers, cellulose derivatives esterified with polybasic acids, and polyvinyl acetate-phthalate.

In some cases, it is desired to provide a medicament with a coating or matrix which can withstand gastric as well as enteric environments and which will release the active ingredient only when the medicament has reached the large intestine and in particular the colon. This may be suitable in treating special colon diseases such as Crohm's disease and several types of colon cancer but also to reach a higher efficacy of medicaments such as corticosteroides, laxatives, vermicides and the like, thus allowing smaller doses to be sufficient. Most of the cited coating and matrix materials are unsuitable for this purpose, however, because they will dissolve or disintegrate already in the small intestine.

It has been suggested already to coat medicaments with polymers which have been cross-linked with azoaromatic groups. Such polymers would protect the medicament against

absorption within the stomach and the small intestine but would release the medicament in the colon as a result of disintegration through activity of the microflora present therein. Reported data show, however, that large individual differences are existing in practice (Saffran et al, Science, 1986, 233, 1081).

In accordance with the invention, it has been found that certain copolymers of (meth)acrylic acid and alkyl or hydroxyalkyl (meth)acrylate will fulfill the object in view because they are resistent to gastric juice and will dissolve or disintegrate only in an environment of pH above 7 such as prevailing in the colon. A precondition is that the ratio of free carboxy groups to esterified carboxy groups in the copolymer is between 1:4.5 and 1:3, the limiting values of this range being excluded. The copolymer has become insoluble in any intestinal juice at a value of 1:4.5 for said ratio and the copolymer will dissolve or disintegrate already prior to reaching the colon at a value of 1:3.

It has to be noted that several copolymers of (meth)acrylic acid and alkyl (meth)acrylate, suitable for use as gastric-resistent coating or matrix material for medicaments, are already known in the art and commercially available. However, the available copolymers of this type have a value of 1:1 or 1:2.3 for the ratio of free carboxy groups to esterified carboxy groups and will start to disintegrate already in the small intestine at pH 6, and pH 7 respectively, thus rendering them unsuitable for the purposes of the invention.

So, the invention provides a coating or matrix material for medicaments which comprises a copolymer of (meth)acrylic acid and alkyl or hydroxyalkyl (meth)acrylate wherein the ratio of free carboxy groups to esterified carboxy groups is between 1:4.5 and 1:3, the limiting values of this range being excluded.

The copolymers meant herein are composed of acrylic acid or methacrylic acid units and of alkyl acrylate, hydroxyalkyl acrylate, alkyl methacrylate or hydroxyalkyl methacrylate units, in random or ordered sequences. The

alkyl groups will have 1-5 and preferably 1-3 carbon atoms whereas the hydroxyalkyl groups will have 1-5 and preferably 2-4 carbon atoms. Suitable examples are copolymers of methacrylic acid and methyl methacrylate, copolymers of methacrylic acid and ethyl methacrylate as well as copolymers of methacrylic acid and methyl acrylate. However, they should satisfy the condition that the ratio of free carboxy groups to esterified carboxy groups is between 1:4.5 and 1:3.

The invented coating or matrix material may be prepared in general in several ways. Thus, it is possible that preparation is effected by copolymerisation of (meth)-acrylic acid and alkyl or hydroxyalkyl (meth)acrylate in such proportions that the ratio of free carboxy groups to esterified carboxy groups in the end product is between 1:4.4 and 1:3. Such a copolymerisation may be effected conventionally as an emulsion polymerisation.

Another option which is preferred at the moment comprises starting with a copolymer of (meth)acrylic acid and alkyl or hydroxyalkyl (meth)acrylate wherein the ratio of free carboxy group to esterified carboxy groups has a value between 1:1 and 1:3, and partially esterifying the free carboxy groups therein until the ratio of free carboxy groups to esterified carboxy groups is between 1:4.5 and 1:3. Esterification may be effected with alkyl groups or hydroxyalkyl groups, alkyl groups having 1-3 carbon atoms and hydroxyalkyl groups having 2-4 carbon atoms being again preferred. Any suitable agent for introducing alkyl or hydroxyalkyl groups may be used as an esterification agent. Diazomethane is a preferred agent for the introduction of methyl groups.

The invented copolymer may be used as a coating material for medicaments by spraying a solution of that copolymer in an organic solvent onto the medicament which may have the form of a fine powder, a granulate or tablets or which may b contained in gelatin capsules. After removal of the solvent by drying, the polymer remains as a coating layer at the surface of the medicament.

In another utilisation, the copolymer is mixed with the medicament in such a way that it will form a matrix having the medicament embedded therein. In both cases, the medicament will be released as soon as the copolymer has passed the stomach and has reached the colon after oral administration.

In the case that the copolymer is used as a coating material for medicaments, several variants are possible which may lead to a controlled release of medicament in the colon or in other parts of the gastro-intestinal tract. Thus, various degrees of delay can be obtained by varying the solubility characteristics of the coating layer, simply by blending copolymers having different values for the ratio of free carboxy groups to esterified carboxy groups. Further, it is possible to provide different parts or particles of the medicament with coating layers of varying thickness so as to result into a phased or gradual release. The required thickness can be determined by routine experiments but it should be noted that a thickness of at least 10 μm is normally needed for providing sufficient mechanical strength. The coating layer may consist as a whole of a copolymer according to the invention, but as an alternative, this copolymer may form a "window" in an inert coating layer or it may lend temporary strength to a coating layer which is weak in itself. Further, the copolymer-coated medicament may be provided with a conventional gastric-resistent coating layer and may optionally have an active ingredient between the two coating layers; in that way, it is possible to ensure release of a medicament in the stomach and/or in the small intestine, and release of a medicament in the colon as well. The material coated with a coating layer may be a solid or an aqueous or semi-aqueous liquid, provided that this material does not affect or deteriorate the copolymer.

Example

a) Preparation of a suitable copolymer by methylation.

The starting material of this example was a commercially available copolymer of methacrylic acid and methyl

methacrylate, having about 30% of methacrylic acid units (the ratio of free carboxy groups to esterified carboxy groups being 1:2.3). The acid number was 185 (calculated as mg of KOH per gram of dry solids).

10 grams of this copolymer were suspended in 25 ml of ether. 50 ml of an ethereal solution of diazomethane (concentration 0.425 M) was added thereto and the mixture was stirred at room temperature for 5 minutes. The resulting product was filtered off, dried in the air and completely dried at 50°C in vacuo. This product had an acid number of 120 which corresponds to a value of 1:3.5 for the ratio of free carboxy groups to esterified carboxy groups.

In a similar way, a product having an acid number of 100, corresponding to a value of 1:4 for the ratio of free to esterified carboxy groups, was obtained from 10 grams of starting copolymer and 38 ml of diazomethane solution.

b) Solubility in vitro.

A solution of the resulting copolymer in acetone was cast onto a glass plate and dried thereon to obtain a film product. Pieces of the isolated film were introduced in glass tubes containing buffer solutions of different pH values (ranging from pH 7 to pH 8). The time period necessary for the film to dissolve was measured. The copolymer having an acid number of 120 did not dissolve after staying 4 hours in a medium of pH 7 but had been dissolved after 2 hours stay in a medium of pH 7.4. The copolymer having an acid number of 100 did not dissolve after staying 4 hours at pH 7 or pH 7.4 but had been dissolved after 2 hours stay at pH 8.

c) Disintegration of the copolymer <u>in vitro</u>

Pieces of the isolated film were introduced as a membrane between the donor compartment and the acceptor compartment of a series of diffusion cells. Both compartments of each cell contained an electrolyte of certain pH (ranging from pH 7 to pH 8 for the whole s ries of cells) and caffeïn had been added as a marker to each donor compartment. The progression of caffeïn concentration within the acceptor compartment of each cell was measured spectrop-

hotometrically during a period of several hours. A sudden increase of the caffein concentration as measured was regarded as indicating the disintegration of the film used as a membrane.

The film from copolymer of acid number 120 disintegrated after 13 hours at pH 7, after 144 minutes at pH 7.5, and after 50 minutes at pH 8.

The film from copolymer of acid number 100 disintegrated after 12 hours at pH 7.5 and after 200 minutes at pH 8.

d) Behaviour <u>in vivo.</u>

Gelatin capsules were filled with pellets of Amberlite IR-120-P (Sigma, USA) ion exchanger which had been marked with [^{111}In] indium chloride and a small amount of [1-^{14}C] cholylglycine. Thereafter, the capsules were coated with a film of methylated copolymer.

The capsules were orally administered to test persons and their course through the body was scintigraphically monitored with the aid of a gamma-ray camera and an image screen. The time needed by the capsules to reach the colon without disintegration was measured.

Moreover, a breath test on radio-active CO_2 was carried out. If the coating layer of the capsule disintegrates after a certain residence time in the colon, the contents of the capsule will be released and radio-active cholylglycine will be metabolised by the intestinal flora whereupon [^{14}C] CO_2 is breathed out. During the breath test, CO_2 was captured by hyamine dissolved in ethanol. The concentration of [^{14}C] CO_2 in the hyamine solution was determined with a Packard counter.

Capsules having a coating layer from copolymer of acid number 120 reached the colon after 300 minutes (average of 6 test persons) and radio-active CO_2 was measured in the test persons' breath after 70 minutes residence time in the colon, which indicates a disintegration of the coating layer.

Capsules having a coating layer of 2.1 mg/cm^2 from copolymer of acid number 100 reached the colon without

disintegration after 300 minutes (one test person) and disintegrated after 600 minutes (detection of radio active CO_2 in the person's breath and visual observation on the image screen).

Capsules having a coating layer of 5.3 mg/cm^2 from copolymer of acid number 100 also reached the colon after 300 minutes (one test person) but did not disintegrate.

The conclusion from these tests must be that the copolymer of acid number 120 (ratio 1:3.5) is suitable for the purposes of the invention whereas the copolymer of acid number 100 is substantially unsuitable for such purposes.

C L A I M S

1. A coating or matrix material for medicaments, said material comprising a copolymer of (meth)acrylic acid and alkyl or hydroxyalkyl (meth)acrylate wherein the ratio of free carboxy groups to esterified carboxygroups is between 1:4.5 and 1:3, the limiting values of this range being excluded.

2. A coating or matrix material as claimed in claim 1, characterized in that the alkyl or hydroxy alkyl (meth)-acrylate in said copolymer is a C_{1-3} alkyl or a C_{2-4} hydroxy-alkyl (meth)acrylate.

3. A method of preparing a coating or matrix material for medicaments, characterized by preparing a copolymer of (meth)acrylic acid and alkyl or hydroxyalkyl (meth)acrylate wherein the ratio of free carboxy groups to esterified carboxy groups is between 1:4.5 and 1:3, the limiting values of this range being excluded.

4. A method as claimed in claim 3, characterized in that the preparation is effected by copolymerisation of (meth)acrylic acid and alkyl or hydroxyalkyl (meth)acrylate in such proportions that the ratio of free carboxy groups to esterified carboxy groups in the end product is between 1:4.5 and 1:3.

5. A method as claimed in claim 3, characterized by starting with a copolymer of (meth)acrylic acid and alkyl or hydroxyalkyl (meth)acrylate which has a value between 1:1 and 1:3 for its ratio of free carboxy groups to esterified carboxy groups, and partially esterifying the free carboxy groups therein until the ratio of free carboxy groups to esterified carboxy groups is between 1:4.5 and 1:3.

6. A method as claimed in claim 5, characterized in that esterification is effected by introducing C_{1-3} alkyl or C_{2-4} hydroxyalkyl groups.

7. A method as claimed in claim 5, characterized in that esterification is effected by introducing methyl groups with the aid of diazomethane.

8. A medicament provided with a coating or matrix of a material as claimed in claim 1.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 91/02046

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K9/20; A61K9/32; A61K9/48; C08F8/14
C08F220/12

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K ; C08F

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
Y	WO,A,8 300 435 (J. B. TILLOTT LTD) 17 February 1983 see claims 1-11	1-6,8
Y	GB,A,907 309 (ABBOTT LABORATORIES) 3 October 1962 see page 2, column 1; claims 1-16	1-6,8
X	CHEM. ZENTRALBLATT vol. 50, no. 1864, 1965, I. UTSUMI: 'SCHUTZUBERZÜGE' see abstract	1-4,8
A	DATABASE WPIL, NO. 82-96687E, DERWENT PUBLICATIONS LTD, (LONDON, GB) & JP, A, 57161859 (CANON K. K.) 5 OCTOBER 1982 see abstract	7

-/—

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
08 JANUARY 1992	21. 01. 92
International Searching Authority	**Signature of Authorized Officer**
EUR PEAN PATENT OFFICE	PERMENTIER W.A

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	EP,A,0 383 967 (DOJIN IYAKU-KAKO CO.) 29 August 1990 see claims 1-9	1
A	DE,A,1 944 693 (BANKER) 30 April 1970 see claims 1-14	1
A	GB,A,1 159 236 (NATTERMANN & CIE) 23 July 1969 see claims 1-10	1
A	EP,A,0 143 608 (ALLIED COLLOIDS LTD) 5 June 1985 see claims 1-14	1
A	EP,A,0 143 935 (BELLAND AG) 12 June 1985 see claim 1	1

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. EP 9102046
SA 52396

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 08/01/92

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-8300435	17-02-83	AU-B-	551173	17-04-86
		AU-A-	8732482	22-02-83
		CA-A-	1172570	14-08-84
		EP-A,B	0097651	11-01-84
		GB-A,B	2123695	08-02-84
GB-A-907309		BE-A-	593353	
		DE-B-	1250309	
		FR-A-	1248796	
		NL-A-	248552	
EP-A-0383967	29-08-90	US-A-	4948581	14-08-90
DE-A-1944693	30-04-70	FR-A-	2017311	22-05-70
		GB-A-	1278817	21-06-72
		US-E-	RE28316	21-01-75
		US-A-	3629392	21-12-71
GB-A-1159236	23-07-69	DE-A-	1617671	01-04-71
		FR-A-	1559913	14-03-69
		US-A-	3592945	13-07-71
EP-A-0143608	05-06-85	AU-B-	584595	01-06-89
		AU-A-	3674784	13-06-85
		AU-B-	582131	16-03-89
		AU-A-	3678284	13-06-85
		CA-A-	1245105	22-11-88
		EP-A,B	0163698	11-12-85
		EP-A,B	0162910	04-12-85
		JP-A-	60132642	15-07-85
		WO-A-	8502408	06-06-85
		WO-A-	8502443	06-06-85
		US-A-	4656205	07-04-87
		US-A-	4660645	28-04-87
EP-A-0143935	12-06-85	DE-A-	3335954	04-04-85
		AU-B-	581411	23-02-89
		AU-A-	3263384	18-04-85
		AU-B-	581626	02-03-89
		AU-A-	3383684	26-04-85

EPO FORM P079

For more details about this annex : see fficial Journal of the European Patent Office, No. 12/82

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9102046 SA 52396

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 08/01/92

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0143935		CA-A- 1256272	27-06-89
		CA-A- 1241500	30-08-88
		EP-A,B 0143894	12-06-85
		JP-A- 60108403	13-06-85
		JP-A- 60155212	15-08-85
		US-A- 4870148	26-09-89
		US-A- 4612355	16-09-86